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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/243,102	02/02/99	MACLACHLAN I	16303-73-2

020350 HM12/0410
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EXAMINER	
ZARA, J	
ART UNIT	**PAPER NUMBER**
1635	5

DATE MAILED: 04/10/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File Copy

Office Action Summary

Application No.	Applicant(s)
09/243,102	MacLachlan et al
Examiner	**Group Art Unit**
Zara, Jane	1635

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-34 is/are pending in the application.

Of the above, claim(s) 29-34 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-28 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-28, drawn to a method of treating a neoplasm, classified in class 514, subclass 44.

II. Claims 29-34, drawn to a method to sensitize cells, classified in class 435, subclass 455.

The inventions are distinct, each from the other because of the following reasons: Inventions of Group I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are drawn to materially different methods, comprising different method steps with resultant different effects.

Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

During a telephone conversation with Eugenia Garrett-Wackowski on January 18, 2000 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-28, drawn to a method of treating a neoplasm. Affirmation of this election must be made by

applicant in replying to this Office action. Claims 29-34 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 (e) as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78). On the declaration and transmittal forms of the instant application, priority is claimed to U.S. Provisional Applications Serial No.'s 60/112,384 and 60/073,598. The first paragraph of the specification makes reference to a related, co-pending U.S Application which claims priority to U.S. Provisional Applications Serial No.'s 60/112,384 and 60/073,598. As written, it is not clear that the instant application also claims priority to U.S. Provisional Applications Serial No.'s 60/112,384 and 60/073,598. To properly claim priority to U.S. Provisional Applications Serial No.'s 60/112,384 and

60/073,598, specific reference should be made to the claim and it should be done in the first sentence of the specification.

Specification

The disclosure is objected to because of the following informalities: In the second sentence of the first paragraph of the specification reference is made to a related, co-pending U.S. Application, but the serial number is not provided and, in its place, there is a blank line.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-7, 11 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is indefinite due to the recitation of "therapeutic polypeptides and therapeutic polynucleotides". It is not clear how an expressible gene necessarily encodes a "therapeutic" polynucleotide.

Claim 4 is indefinite because of the recitation "said gene is exogenous". The term "exogenous" must be defined.

Claim 5 is indefinite because of the recitation "suicide enzymes". The term "suicide enzymes" must be defined and adequate representative examples must be provided.

Claim 6 is indefinite because of the recitation "analogs". The term "analogs" must be defined, with appropriate examples given.

Claim 7 is indefinite because of the recitation "homologous". The term "homologous" must be defined.

Claim 11 is indefinite because of the recitation "protonatable lipid". This term must be more explicitly defined.

Claim 16 is indefinite because of the recitation "substantially devoid", and should be replaced with a more quantitative term.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is drawn to a method of treating a neoplasia in a mammal comprising the administration of a serum-stable nucleic acid lipid particle whereby the nucleic acid encodes an expressible homologous or exogenous gene and said nucleic acid is fully encapsulated within the lipid portion of the particle, which treatment further comprises the administration of a chemotherapeutic agent, and whereby administration of the lipid particle, nucleic acid and chemotherapeutic agent occurs by injection at a site distal to said neoplasia and some therapeutic effect is obtained.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and use the invention. This determination is based on several factors which, when considered together, illustrate that the art of gene delivery and expression is in its infancy and highly unpredictable. The discussion is also based on references whose teachings show that, despite a tremendous amount of experimentation by highly skilled artisans, in the field of gene delivery and expression in vivo there remain significant hurdles and a high level of unpredictability. In the face of art-recognized hurdles and unpredictability, the specification must therefore include enough detailed teachings to enable the skilled artisan to navigate the art-recognized pitfalls and surmount the hurdles known in the art to make and use the claimed invention.

The nature of the invention. Methods of delivering nucleic acids to target cells in vivo fall into the broad area known as gene therapy methods. The delivery of nucleic acids to target cells in a whole organism shares many of the obstacles recognized for other gene therapy

methods because successful therapy methods are for the most part based on the ability to deliver exogenous nucleic acids to cells or tissues of interest and furthermore are based on sufficient levels of exogenous gene expression.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of gene delivery . While Crystal points to the advantages of plasmid-liposome complexes as gene transfer vectors, for instance, the disadvantages include their general inefficiency at achieving successful gene transfer and a general lack of available data regarding repetitive administration of liposomes of DNA to whole organisms (page 405, second paragraph). Schofield et al also teach advantages of liposome delivery of genes in vivo, although many of the details regarding cell targeting, cell entry and gene expression in target cells remain highly speculative. Schofield et al caution their readers about the *significant variations that exist between animals*, and state that only limited conclusions could be drawn from animal studies which may be applied to the treatment of humans (pages 61-64). Verma et al teach the problems of gene delivery in whole organisms using non-viral vector approaches, including liposomes as delivery agents, and state that such approaches suffer from limitations relating to poor efficiency of delivery and the transient expression of delivered genes (page 239, second paragraph from the end). Friedmann teaches that gene transfer by liposomes is much less efficient than virus-mediated transfer (page 100, last paragraph-page 101, first paragraph), while, according to Friedmann, the gene therapy field as a whole currently lacks convincing therapeutic benefit (page 96). Branch and Crooke teach that

the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of in vivo inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke).

While these references acknowledge the usefulness of gene therapy including lipid mediated delivery and the possibility of developing efficacious strategies in the future, they also illustrate that there are numerous obstacles to successful gene therapy which current methods still must overcome. As such, the disclosed utilites of the present specification which are drawn to gene delivery methods are credible. The present rejection, therefore is not for lack of utility, but rather for lack of enablement for the methods claimed.

The amount of direction or guidance presented in the specification and the presence or absence of working examples. Applicants have not provided guidance in the specification toward lipid mediated gene delivery in a mammal which would avoid the technical obstacles recognized in the art as described above.

The specification teaches the delivery and expression of a single gene (hyper TK) in combination with the administration of the antineoplastic agent ganciclovir in immunocompromised mice bearing intradermally seeded fibrosarcoma tumor cells or colorectal tumor cells, which administration comprises use of a lipid mediated delivery system comprising a combination of DODAC, DOPE and PEG-C8 or C20, whereby the nucleic acid is encapsulated by the lipid particle, which is injected at a site distal to the neoplasia, whereby a reduction of

tumor size and an increase in survival time is observed in treated mice. The specification fails to teach the successful delivery and expression of expressible genes in any immunologically competent organisms such that treatment effects are provided. The specification fails to teach the successful delivery and expression of expressible genes intended for delivery in vivo, which genes have not been mutated to have higher catalytic efficiency upon expression in a model system whereby treatment effects can be provided in immunologically competent organisms, and further where treatment effects are provided in organisms other than immunodeficient mice.

The breadth of the claims the quantity of experimentation. The breadth of the claims is very broad. They are drawn to the delivery of any gene in any vector, in combination with the delivery of any antineoplastic agent using any lipid particle or any combination of lipids. The claims are also drawn to the treatment of any neoplasm in any mammal. In order to practice the invention over the scope claimed, the skilled artisan would have to practice trial and error experimentation to determine the appropriate genes, antineoplastic agents and delivery molecules, as well as appropriate combinations and dosages of molecules used. The quantity of experimentation required to practice the invention as claimed would require the de novo determination of accessible target sites, formulations to target appropriate cells and/or tissues harboring a particular neoplasm in a particular organism, whereby that organism is immunocompetent, as well as the de novo determination of toxicity and other side effects in a particular organism for a particular gene, for a particular antineoplastic agent and for a particular lipid particle, or for any combinations thereof. Since the specification fails to provide any

particular guidance in this regard, and since determination of these factors for a particular neoplasm in a particular organism is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (703)-***306-5820***. The examiner's supervisory primary examiner is George Elliott who can be contacted at (703)-***308-4003.***

Remy Yucel

REMY YUCEL, PH.D
PATENT EXAMINER

JZ

April 7, 2000